UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/700,817	11/20/2000	Norifumi Tanida	K0448/7007	2886

7590 09/10/2003

John R Van Amsterdam
Wolf Greenfield & Sacks
Federal Reserve Plaza
600 Atlantic Avenue
Boston, MA 02210-2211

EXAMINER	
SCHNIZER, RICHARD A	
ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 09/10/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/700,817	TANIDA ET AL.	
	Examiner	Art Unit	
	Richard Schnizer, Ph. D	1635	

-- The MAILING DATE of this communication app ars on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *31 December 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *1* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 1-18 are pending and under consideration in this Office Action.

Claim Objections

Claims 12, 13, 14, and 16 are objected to. These claims, as written require the use of every disintegrator, saccharide, excipient, or binder listed, because the listed items are not presented as alternatives. A review of the specification indicates that these items are intended as alternatives. For example, although claim 12, as written requires the use in a single composition of every disintegrator listed, the specification indicates that these disintegrators are intended as alternatives. For the purpose of examination, claims 12-14 and 16 have been interpreted as reciting Markush groups of alternative species.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-18 are indefinite because the recite "the core" without antecedent basis. It is conceivable that a solid preparation could have several "cores", so it is unclear to which core the claim refers. It is also unclear what it is that must have

"releasability in the lower digestive tract", it could be the solid composition, the core, or the gene related drug. Furthermore, the clause "wherein the coating, not disintegrating in the small intestines and has a double coated structure" is ungrammatical such that it lacks any clear meaning. If Applicant intended to claim a coating that does not disintegrate in the small intestines and which has a double coated structure, then an amendment to that effect is suggested.

Claims 1, 15, and 18 are indefinite because it is unclear as to whether the "core" must contain "a gene-related drug", or if the gene related drug may be anywhere in the solid preparation.

Claims 1-17 are also indefinite because the metes and bounds of "a gene-related drug" are unclear. More particularly, it is unclear what Applicant intends by the term "gene". The specification does not define the term, there is no single art-recognized definition for the term, and it is used in the art to refer to different concepts. On the one had it is used by classical geneticists to describe a genetic unit that confers a phenotype on an organism. Alternatively it is understood to mean a cistron, or in some cases only an open reading frame. It is unclear which definition Applicant intends. The specification gives examples of what is embraced by "a gene-related drug" at page 6, but the specification does not clearly exclude other compounds that could be construed as gene related. For example, inasmuch as protein drugs are encoded by genes, they can reasonably be considered to be gene-related drugs, as could compounds that influence gene expression such as signaling molecules. Based on the passage from page 6, line16 to page 7, line 12 , it appears that Applicant may intend polypeptides to

be included as gene related drugs. See specifically, at page 6, lines 16-23, the phrases "suppressive type gene pharmaceuticals such as TNF-alpha", etc. "or expression type gene pharmaceuticals such as IL-2" etc. This language implies that a protein can be a gene pharmaceutical within the meaning of the claims and specification. Further, US Patent 6,214,378 describes CGRP (calcitonin gene-related peptide) as a pharmaceutically active substance. See column 3, line 38. Clearly CGRP is considered to be a drug, and its name indicates it is related to a gene.

Claim 15 is indefinite because the metes and bounds of "modified compounds thereof" and "compounds thereof" are unclear. The specification fails to define what is considered to constitute a modification, and it is unclear if there is intended to be a distinction between DNA and RNA compounds and compounds thereof.

Claim 17 is indefinite because it lacks a verb and is not a complete sentence.

Claim 18 is indefinite because it recites "the gene-related drugs" without proper antecedent basis. Claim 1, from which claim 18 depends allows for only a single gene related drug, so there is no antecedent basis for the plural "drugs."

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1 and 18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compositions comprising drugs for delivery to the lower digestive tract such as polypeptides, ketoprofen, oligonucleotides, antisense

nucleic acids, antisense oligonucleotides, ribozymes, plasmids, cosmids, and yeast artificial chromosomes, does not reasonably provide enablement for compositions for delivery to the lower digestive tract comprising drugs that are triple helix forming oligonucleotides, decoys, phage, P1 phage, or non-artificial chromosomes. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Claim 18 is drawn to a solid preparation for oral administration comprising a drug, wherein the drug may be a triple helix forming oligonucleotide, decoy, phage, P1 phage, or non-artificial chromosome. A review of the specification shows that the composition is designed to deliver the drug to the lower digestive tract. The specification does not define the term "drug". Steadman's Medical Dictionary (24th Edition, 1982) defines "drug" as "[a] therapeutic agent; any substance, other than food, used in the prevention, diagnosis, alleviation, treatment, or cure of disease in man and animal." In order to enable the claims, the specification in combination with the prior art must teach how to use in the lower digestive tract a triple helix forming oligonucleotide, decoy, phage, P1 phage, or non-artificial chromosome as a therapeutic agent, or as a substance used in the prevention, diagnosis, alleviation, treatment, or cure of disease in man or animal.

A search of the prior art indicated that a triple helix forming oligonucleotides, decoys, phages, P1 phages, and non-artificial chromosomes were not routinely used as drugs in the lower digestive tract, in fact no reference supporting such a use was found. While Applicant is not required to disclose that which is well known in the art, there is an

obligation to disclose critical elements of the invention as well as how to use these elements. In Genentech, Inc, v Novo Nordisk A/S, the court found that when the specification omits any specific starting material required to practice an invention, or the conditions under which a process can be carried out, there is a failure to meet the enablement requirement. See 42 USPQ2d 1001.

> It is true, as Genentech argues, that a specification need not disclose what is well known in the art. See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific starting material or of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. This specification provides only a starting point, a direction for further research.

In this case, the identification of triple helix forming oligonucleotides, decoys, phages, P1 phages, or non-artificial chromosomes that can act as drugs in the lower digestive tract cannot be considered a minor detail that can be omitted in the process of providing an enabling disclosure, and one of skill in the art would have to perform undue experimentation to make or use the invention as intended.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-14 and 16 are rejected under 35 U.S.C. 102(a) and 102(e) as being anticipated by Okayama et al (US Patent 5,654,004, issued 8/5/97), as evidenced by Kawamoto et al (US Patent 6,180,621, issued 1/30/01), and Shimuzu et al (US Patent 6,586,004, issued 7/1/03).

This rejection is based on an interpretation of the claims in which the term "gene-related drug" is considered to embrace polypeptides encoded by genes as well as compounds that affect gene expression.

Okayama teaches oral pharmaceutical preparations for releasing gene-related drugs" in the lower digestive tract. The composition comprises a core containing either a polypeptide drug such as calcitonin, or a drug that affects gene expression such as ketoprofen, wherein the core is surrounded by an inner coat made of a cationic copolymer and an outer coat made of an anionic copolymer. See abstract; column 3, lines 36-55; and column 3, lines 60 to column 4, line 25. Okayama exemplifies at column 7, lines 10-15 a ketoprofen-containing granule with a core comprising ketoprofen (20%), lactose (25%), corn starch (30%), crystalline cellulose (20%), and hydroxypropyl cellulose (5%). The functions of the lactose, corn starch, crystalline cellulose, and hydroxypropylmethyl cellulose in this composition are not clearly stated. However, Kawamoto teaches that lactose, corn starch, and crystalline cellulose function in oral delivery compositions as excipients, binders, and disintegrators interchangeably.

See column 11, lines 34-60. Also Shimuzu teaches that hydroxypropyl cellulose is a disintegrator. See column 6, lines 43-49. It is also apparent from instant claims 12, 14, and 16 that Applicant considers lactose, starch, and crystalline cellulose to be disintegrators, considers at least starch, crystalline cellulose, and lactose to be excipients, and considers at least starch and hydroxypropyl cellulose to be binders. In view of the forgoing, claims 5-11 are anticipated. For example, claim 5 is anticipated if one considers the binder to be one of corn starch, crystalline cellulose, and hydroxypropyl cellulose, and the excipient to be one of the other two of these components. Claim 6 is anticipated if one considers any one of lactose, corn starch, or crystalline cellulose, to be the saccharide. Note that the specification defines each of these compositions as saccharides in the paragraph bridging columns 4 and 5. Claims 7 and 8 are anticipated if the disintegrator is hydroxypropyl cellulose. Claim 9 is anticipated if the excipient is hydroxypropyl cellulose. Claims 10 and 11 are anticipated because the gene-related drug (ketoprofen) is present at 20 % (w/w). Claims 12-14 and 16 are not included in this rejection because these claims require the presence in the composition of all of the listed excipients, binders, disintegrators, or saccharides, rather than just one of the listed compounds, and Okayama does not teach a single composition comprising each of these excipients, binders, disintegrators, or saccharides. Claims 12-14 and 16 are anticipated at least because the composition of Okayama comprises lactose and crystalline cellulose. Lactose can be considered to be either the saccharide of claim 13, or the excipient of claim 14. Crystalline cellulose is

recited in each of claims 12, 14 and 16 as functioning as a disintegrator, an excipient, or a binder, respectively.

The various species recited in claims each of claims 12-14 and 16 are considered to be obvious in view of each other. Should Applicant amend the claims to delete species that are explicitly recited by the cited art, while leaving the non-anticipated species extant, the Examiner will make a FINAL obviousness rejection. For evidence that the species are obvious in view of each other see e.g. Kawamoto and Shimuzu, above.

Thus Okayama anticipates the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 15, and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over of Bennett et al (US Patent 6,096,722, issued 8/1/00) in view of Okayama et al (US Patent 5,654,004, issued 8/5/97).

Bennett teaches a method for treating inflammatory bowel disease, e.g. colitis, by administering to the colon a composition comprising an antisense DNA or RNA oligonucleotide drug. See e.g. claim 18 at column 114, lines 34 and 35; and column 9, lines 14-16. The oligonucleotides may be modified or bound to a carrier. See e.g.

paragraph bridging columns 9 and 10, and column 12, lines 27-54. Administration may be by the oral route. See column 16, lines 34-37, column 17, lines 8-21 and column 18, lines 60-65.

Bennett does not teach a solid preparation comprising a drug-containing core wherein the core is surrounded by an inner coat made of a cationic copolymer and an outer coat made of an anionic copolymer.

Okayama teaches oral pharmaceutical preparations for releasing drugs in the lower digestive tract. The composition comprises a core containing a drug, wherein the core is surrounded by an inner coat made of a cationic copolymer and an outer coat made of an anionic copolymer. See abstract; column 3, lines 36-55; and column 3, lines 60 to column 4, line 25.

It would have been obvious to one of ordinary skill in the art at the time of the invention to formulate the drug of Bennett in the delivery preparation of Okayama. One would have been motivated to do so because Bennett teaches that the antisense may be or bound to a carrier and administered orally, and the carrier preparation of Okayama is specially formulated for oral administration to avoid degradation in the stomach and small intestines, so that most of the drug is delivered to the large intestine, the site of colitis. See column 2, lines 53-59 of Okayama.

Thus the invention as a whole was prima facie obvious.

Claims 1, 15, and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over of Kufe et al (US Patent 5,874,415, issued 2/23/99), in view of Okayama et al (US Patent 5,654,004, issued 8/5/97).

Kufe teaches a method of treating colon cancer by administration of plasmid DNA drug encoding either a suicide gene or antisense RNA. See e.g. claim 4 at column 17, or claim 15 at column 18, and column 2, lines 21-33. Deliver may be by the oral route. See column 6, lines 22-28 and 38-42.

Kufe does not teach a solid preparation comprising a drug-containing core wherein the core is surrounded by an inner coat made of a cationic copolymer and an outer coat made of an anionic copolymer.

Okayama teaches oral pharmaceutical preparations for releasing drugs in the lower digestive tract. The composition comprises a core containing a drug, wherein the core is surrounded by an inner coat made of a cationic copolymer and an outer coat made of an anionic copolymer. See abstract; column 3, lines 36-55; and column 3, lines 60 to column 4, line 25.

It would have been obvious to one of ordinary skill in the art at the time of the invention to formulate the drug of Kufe in the delivery preparation of Okayama. One would have been motivated to do so because the preparation of Okayama is specially formulated to avoid degradation in the stomach and small intestines, so that most of the drug is delivered to the large intestine, the site of he disease that is treated in the method of Kufe. See column 2, lines 53-59 of Okayama.

Thus the invention as a whole was prima facie obvious.

Claim 18 is also rejected under 35 U.S.C. 103(a) as being unpatentable over of Kufe et al (US Patent 5,874,415, issued 2/23/99) and Okayama et al (US Patent 5,654,004, issued 8/5/97) as applied to claims 1, 15, and 18 above, and further in view of Soykan et al (US Patent 6,151,525, issued 11/21/00).

The teachings of Kufe and Okayama are discussed above and can be combined to render obvious a solid preparation comprising a plasmid containing a gene drug-containing core wherein the core is surrounded by an inner coat made of a cationic copolymer and an outer coat made of an anionic copolymer.

These references do not teach a cosmid or a YAC comprising a gene drug.

Soykan teaches that plasmids, cosmids, and YACs are recognized equivalents in the art of gene delivery. See column 7, line 64 to column 8, line 5. MPEP 2144.06 indicates that when it is recognized in the art that elements of an invention can be substituted, one for the other, while retaining essential function, such elements are art-recognized equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). Furthermore, MPEP 2144.07 indicates that the selection of a known material based on its suitability for its intended use supports the determination of prima facie obviousness. See also Sinclair & Carroll Co. v. Interchemical Corp., 325 U.S. 327, 65 USPQ 297 (1945). The species "chromosome" recited in claim 18 is considered to be obvious over the cited art to the extent that a yeast artificial chromosome is considered to be a chromosome.

Thus the invention as a whole was prima facie obvious.

Claims 1 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bennett et al (US Patent 6,096,722, issued 8/1/00) in view of Okayama et al (US Patent 5,654,004, issued 8/5/97), and Rossi et al (Methods 5: 1-5, 1993).

The combination of Bennett and Okayama is discussed above. These references can be combined to render obvious a composition comprising a core containing a drug, wherein the core is surrounded by an inner coat made of a cationic copolymer and an outer coat made of an anionic copolymer, and wherein the drug is an antisense RNA.

These references do not teach a ribozyme.

Rossi teaches that ribozymes are an extension of non-enzymatic antisense technology, and that either ribozymes or non-enzymatic antisense can be used to inhibit gene expression, noting that "[f]or most applications for which an antisense RNA is contemplated, it should be possible to utilize a ribozyme in parallel or in place of the antisense." MPEP 2144.06 indicates that when it is recognized in the art that elements of an invention can be substituted, one for the other, while retaining essential function, such elements are art-recognized equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). Furthermore, MPEP 2144.07 indicates that the selection of a known material based on its suitability for its intended use supports the determination of prima facie obviousness. See also Sinclair & Carroll Co. v. Interchemical Corp., 325 U.S. 327, 65 USPQ 297

(1945). Thus it would have been obvious to one of ordinary skill in the art to substitute a ribozyme for the antisense of Bennett, and the invention as a whole was prima facie obvious.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 703-306-5441. The examiner can normally be reached Monday through Friday between the hours of 6:20 AM and 3:50 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John Leguyader, can be reached at 703-308-0447. The FAX numbers for art unit 1632 are 703-308-4242, and 703-305-3014. Additionally correspondence can be transmitted to the following RIGHTFAX numbers: 703-872-9306 for correspondence before final rejection, and 703-872-9307 for correspondence after final rejection.

Inquiries of a general nature or relating to the status of the application should be directed to the Patent Analyst Trina Turner whose telephone number is 703-305-3413.

DAVE T. NGUYEN
PRIMARY EXAMINER

Richard Schnizer, Ph.D.